‘‘DESIGN & DEVELOPMENT OF NUTRITIONAL FORMULATON FOR METABOLIC DISORDER ’’

A SYNOPSIS

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ABSTRACT:

Metabolic disorders are characterized by the inability to properly utilize and/or store energy, with the most prominent metabolic disorder being diabetes. The overall objective of this study is to prepare such a nutritional formulation this should provide macronutrients & micronutrients to treat metabolic disorder. Design & development of nutritional formulation which fulfill metabolic disorder particularly present investigation on the diabetes mellitus. Evidence based cost effective nutritional formulation will made available for society. Standard pharmacological treatment of allopathic medicine having several side effects, health complications & this is driving to search natural approaches. These compounds include macronutrients, micronutrients & active chemical constituents. Based on strength of available evidence regarding such nutritional formulation should be used in the prevention & cure of diabetes mellitus. Therefore, the present study is aimed to design & development of nutrition formulation for metabolic disorder by using effective methodology.

Keyword: metabolic disorder, diabetes, nutrients, phytochemicals, HR-LCMS, pre-clinical, clinical study.

1. INTRODUCTION

Metabolic disorders and its associated chronic disorders including cardiovascular diseases and type 2 diabetes are public health concerns in the USA and worldwide. “Good health is an investment in economic growth,” and nutrition is one of the recommended preventive measures to manage these chronic diseases. There are various definitions of metabolic disorders (eg, World Health Organization, the International Diabetes Federation, and the US National Cholesterol Education Program’s Adult Treatment Panel III [NCEP/ATP III]). The most widely used definition (from the NCEP/ATP III) is defined as the presence of three or more of the following metabolic disorders: central obesity (waist circumference: ≥102 cm for men, ≥88 cm for women), dyslipidemia (high-density lipoprotein cholesterol [HDL]: <40 mg/dL for men, <50 mg/dL for women; or triglycerides [TGs] ≥150 mg/dL), hypertension (systolic/diastolic blood pressure ≥130/85 mmHg), and insulin resistance (elevated fasting blood glucose ≥110 mg/dL).(Hua J Kern et al.)

WHO defines diabetes as “a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces”. Insulin is a hormone that regulates blood sugar. A common effect of diabetes

is Hyperglycemia or increased blood sugar. Diabetes causes some serious health issues including blindness, kidney failure, stroke and heart diseases.

Type 1 diabetes occurs when the body produces insufficient quantities of insulin. It is usually detected more in children. Type 2 diabetes occurs when the body does not effectively use the insulin produced. This is very frequently due to lack of physical activity, obesity, or incorrect dietary habits. Gestational diabetes occurs among pregnant women. In about 90 percent of cases, it is Type 2 diabetes that people are suffering from. The occurrence of Type 2 diabetes or Diabetes Mellitus may be prevented or delayed by adopting a healthy lifestyle.

Diabetes can be identified by indicative symptoms – frequent urination, unusual thirst, excessive fatigue and hunger, weight loss, and wounds that take long to heal. Type 2 diabetes, however, may remain unnoticed and patients may not display any signs for years.

A main cause of diabetes mellitus is genetic factors. On an average, Indians are four times more likely to develop diabetes than Europeans, based solely on genetic outlook. Cultural and social factors are no less important. The Indian diet is rich in carbohydrates and saturated fats. A typical Indian diet has more calories and sugar than required by the body. This is the cause of obesity, which in turn leads to diabetes. Urban migration and change in lifestyle is another factor that must be considered in the study of diabetes in India. With rising standard of living becomes the tendency to consume processed sugary foods.

Diabetes Mellitus (DM) is a metabolic syndrome with multifactorial etiology that has a considerable impact on health and its costs, especially in developing countries. Diabetes mellitus (DM) is a disease which is diagnosed by increase in blood sugar concentration. This can be due to deficiency of insulin secretion or of insulin function or both. Patients with diabetes are estimated to amount to more than 366 million in 2030 being more than twice of the rate in 2000. Most of the new cases will be from the developing countries and seemingly Middle East will suffer most from diabetic prevalence till 2020.

Currently, for treatment of T2DM have been developed standard pharmacological treatment which, however, present several side effects, and this is driving people to search natural approaches. The use of natural approaches for the treatment of metabolic diseases, indeed, is currently the most discussed issue, involving public opinion, researcher and physician. Among the main points in favour of the diffusion of natural remedies in the clinical practice, surely emerge the almost total absence of side effects,

contraindications and/or drug-interactions that make these products safe. (Giuseppe Annunziata et al., 2018)

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al. the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease. (Seema A. Kaveeshwar)

Diabetes may causes complications are hypoglycemia, Hyperosmolar, Hyperglycemic State, Ketoacidosis, Foot care, Foot ulcers, Heart disease, High blood pressure, Neuropathy (Nerve damage), Nephropathy (Kidney disease), Retinopathy (Eye disease), Alzheimer's disease, Coeliac disease, High cholesterol, PCOS, Constipation, Erectile dysfunction, Diarrhea, Nocturia, Thrush, UTIs.

Nowadays, different treatments, such as insulin therapy, pharmacotherapy, and diet therapy, are available to control diabetes. There are several types of glucose-lowering drugs that exert anti-diabetic effects through different mechanisms. These mechanisms include stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increasing of peripheral absorption of glucose by biguanides and thiazolidinediones, delay in the absorption of carbohydrates from the intestine by alpha-glucosidase, and reduction of hepatic gluconeogenesis by biguanides.

In the past three decades, despite the significant progress made in the treatment of diabetes, the results of treatment in patients is still far from perfect. These treatments have some disadvantages, including drug resistance (reduction of efficiency), side effects, and even toxicity. For example, sulfonylureas lose their effectiveness after 6 years of treatment in 44% of patients. It is also said that the glucose-lowering drugs are not able to control hyperlipidemia. Potential side effects of common diabetes drugs**,** **Sulfonylureas:** low blood sugar, upset stomach, and skin rash or itching, weight gain, **Biguanides/Metformin:** sickness with alcohol, kidney complications, upset stomach, tiredness or dizziness, metal taste. **Alpha-glucosidase inhibitors:** gas, bloating and diarrhea, **Thiazolidinediones:** weight gain, risk of liver disease, anaemia risk, swelling of legs or ankles, **Meglitinides:** weight gain, low blood sugar. In addition, the side effects of medicines and their interactions with each other in vitro must be considered by

medical staff. (Wesam Kooti1 et al)

Today, many treatments that involve the use of medicinal plants are recommended. Most plants contain carotenoids, flavonoids, terpenoids, alkaloids, glycosides and can often have anti-diabetic effects. The anti-hyperglycemic effects that results from treatment with plants are often due to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or reducing the intestinal absorption of glucose.

Nutritional intervention studies have been focused on reducing dietary fat with no positive results over long-term periods. The carbohydrate content of diets was also reduced in some populations, but obesity prevalence continued to increase. In diets designed to prevent and treat obesity by manipulating energy content, macronutrient distribution was commonly set at 15% protein, <30% lipids, and 50–55% carbohydrates, with reductions in dietary fat and increases in fibers favoured. Although this recommendation seemed to be effective for decreasing energy density and promoting weight loss in the short term, the low level of observed satiety it achieved decreased dietary adherence over longer periods. Monitoring of low-energy diets with these macronutrient proportions revealed that they were often not sustainable for long periods of time. (Itziar Abete et al., 2010).

Diabetes is mainly due to oxidative stress and an increase in reactive oxygen species that can have major effects. Many plants contain different natural antioxidants, in particular tannins, flavonoids, C and E vitamins that have the ability to maintain β-cells performance and decrease glucose levels in the blood. Diseases of the endocrine glands highlight the importance of hormonal and nutritional factors in the regulation of metabolism in human beings. The nutritional alterations affect each and every aspect of the functioning of the endocrine glands leading to serious disorders. The last century was marked by the classical deficiency disorders, such as goiter, cretinism, hypothyroidism, and rickets. Industrialization coupled with increased availability of junk food leads to the epidemic of different nutritional endocrine disorders, such as obesity, metabolic syndrome, and diabetes. (K. V. S. Hari Kumar et al., 2012).

Hippocrates nearly 2,500 years ago, is receiving renewed interest. In particular, there has been an explosion of consumer interest in the health enhancing role of specific foods or physiologically- active food components, so-called functional foods (Hasler, 1998). Clearly, all foods are functional, as they provide taste, aroma, or nutritive value. Within the last decade, however, the term functional as it applies to food has adopted a different connotation—that of providing an additional physiological benefit beyond that of meeting basic nutritional needs.

Several nutraceuticals used in clinical practice have been shown to target the pathogenesis of diabetes mellitus, metabolic syndrome and their complications and to favourably modulate a number of biochemical and clinical endpoints. These compounds include antioxidant vitamins, such as vitamins C and E, flavonoids, vitamin D, conjugated linoleic acid, omega-3 fatty acids, minerals such as chromium and magnesium, α-lipoic acid, phytoestrogens, and dietary fibers. Several areas of concern exist regarding the use of dietary supplements and nutraceuticals in this setting, including product standardization, definition of optimal dosing regimen, potential side effects, drug interactions, and need for evidence-based indications. (G. Davi et al., 2010)

Macronutrient and micronutrient deficiencies are frequently found in subjects with cardiac disease, vascular problems, hypertension and dyslipidemia as a result of genetic environmental interactions, and prescription and over-the-counter drug use. The impact on cardiovascular outcomes and healthcare costs is large. The diagnosis and treatment of these nutrient deficiencies may improve endothelial dysfunction and vascular disease and lower blood pressure. Vascular biology with endothelial activation, inflammation oxidative stress and immune dysfunction of arteries are early events in hypertension-related vascular disease. Proper nutrition, nutraceuticals, vitamins, weight management, exercise and other lifestyle changes, are effective in the management of hypertension in most patients.

Recent researches focus towards studies on nutrientially rich herbal products as they contribute in the maintenance and promotion of health. Besides they are also found to be useful in controlling various disorders such as diabetes, as well in improving immunity. Recent records revealed consumption of multivitamin supplements daily by approximately 20-30% of population indicating high public interest towards the nutraceuticals approach for the maintenance of health and prevention of chronic diseases. (Nithya Devi M. et al., 2014)

2. REVIEW OF LITERATURE

1. Rohit sharma et al (2015)

He had been reported to currently, available conventional options for diabetes mellitus have certain limitations of their own, and options from medicinal plants with antihyperglycemic activities are being searched to meet the need. Antidiabetic properties of *Tinospora cordifolia* are highly appreciated in Ayurveda and even in recent modern researches. Several studies on its extracts (*viz.* immunemodulatory, anti-hyperglycemic, antioxidant, adaptogenic, hepatoprotective, hormone regulator etc.) and isolated

phytoconstituents (like tinosporin, berberine, jatrorrhizine etc.) have reported that it is a preventive and curative antidiabetic herb, which are substantiated by clinical trials. Scattered information pertaining to antidiabetic potential of *Tinospora* is reported.

2. Araujo AJS et al (2018)

He had been reported that oxidative stress plays an important role in the secondary complications of diabetes. Antioxidant supplements from the diet are considered alternatives for the treatment of DM, with ginger (*Zingiber officinale*) being one of them. Its therapeutic effects have action on insulin sensitivity and protect the body from complications caused by diabetes. However, few articles synthesize the beneficial effects of administration of *Z. officinale* on diabetes. For this purpose, a bibliographic research was carried out on the scientific production of the antidiabetic effect of ginger supplementation. The results show that ginger has hypoglycaemic potential and reduce diabetic complications and should, therefore, be considered in the treatment of this disease.

3. Yin J. et al (2008)

In this present work berberine increases insulin receptor expression & improve glucose utility both in vitro & animal model.

4. Hassan Mozaffari- khosravi et al (2014)

In this study the effect of ginger active component is inhibition of hepatic phoshorylase to reduce hepatic glycogenolysis & to increases activity of the enzymes which causes progression of glycogenesis. The herbal properties which are similar to NSAID, it can regulate biochemical pathway which are activated with chronic inflammation such as diabetes.

The daily consumption of 3g of ginger in capsule for 8 weeks by patient with type 2 diabetes mellitus lead to lowering fasting blood sugar & $HbA1_c$ means as well as variation in fasting insulin, insulin resistance, & increases sensitivity of insulin.

5. Whaley Connell A et al (2009)

L-carnitine could improve the outcome of nonalcoholic fatty liver disease, because reduces lipid level, limit oxidative stress, & modulates inflammatory responses. L-carnitine as a cofactor mitochondrial β-fatty acid oxidation to facilitated the transport of long – chain fatty acid across the mitochondrial membrane.

6. Gema (2005)

According to over nutrition is the chronic consumption of more than is necessary for

good health. Specially, over nutrition is the regular consumption of excess calories, fats, saturated fats or cholesterol all of which increases risk for chronic disease like heart disease, cancer, stroke, diabetes, hypertension and the metabolic syndrome. These conditions may also result in poor clinical outcome with increased morbidity and mortality.

7. Kumar et al (2016)

In the current study carried out *tinospora cordifolia* stem powder (50mg/kg body weight) for 15 day in the type 2 diabetes mellitus patients resulted significant decreases in the level of fasting blood sugar, total cholesterol, β-lipoproteins & triglycerides.

8. Sangeetha et al (2011)

The present study reported that *T. cordifolia* attenuated oxidative stress & improved glycemic level by improving insulin secretion in rats.

9. Hua J Kern et al., (2018)

The present study reported that Resveratrol is a polyphenol found in a variety of fruits (eg. grapes, berries, and plums) and may have a beneficial effect on cardiovascular health via its antioxidant properties and regulation of nitric oxide concentrations in the body. Consumption of resveratrol at both 10 and 100 mg/day has been linked to decreased LDL and improved endothelial cell function. 21 Recently, a favourable effect of trans-resveratrol on glucose homeostasis has been reported at a dose of 150 mg/ day over a 1-month intervention period, indicating a potential benefit on insulin sensitivity. In animal studies, resveratrol has also been shown to decrease fat mass via inhibiting adipocyte differentiation and lipid accumulation and to improve energy efficiency via the regulation of brown fat tissue activity.

3. Objectives of research topic:

1. To prepare such a nutritional formulation this should provide macronutrients & micronutrients to treat the metabolic disorder.
2. To design & development of selective, potent, stable and safer novel nutritional formulation for metabolic disorders from the natural products.

PROPOSED HYPOTHESIS:

1. By taking an idea from literature review, we are decided to work on the preparation of nutritional formulation for metabolic disorders.
2. To maintain the health (normal and abnormal condition) minimum daily

requirement of nutrients & micronutrients are required

3. In case of metabolic disorders particularly diabetes mainly physicians may advice to restricted for intake of carbohydrate containing food, this causes nutritional deficiency & may induced worst condition patients health.
4. Macronutrients & micronutrients are major role in the cure & prevention of metabolic disorders by improving immunity and health of microbiota.

4. METHODOLOGY:

1. Collection and Authentication of plants:

Proposed medicinal plants shall be collected from suitable geographical location & authentication of the plants shall be done from department of botany, school of life sciences, S. R. T. M. U. Nanded

2. Standardization of plants material:

Standardization of plants material of authenticated plants shall be done by using following parameters

I. Determination of moisture content or LOD.
II. Determination of Ash value.
III. Determination of Extractive value.

3. Extraction of plants material:

Properly dried plants material shall be grind & converted into powder form, these powdered plants material shall be subjected to extract using suitable solvent. Extracts shall be concentrated under reduced pressure & dried for further process as per requirement.

4. Preliminary phytochemical tests of various extracts:

Preliminary phytochemical tests of various primary & secondary metabolites shall be carried out.

5. Phytochemical investigation & isolation of chemical constituents from plant extract:

The phytochemical shall be separated by column chromatography using different solvents system.

6. Characterization of isolated compound using advanced analytical techniques:

UV, NMR, IR, MASS & HR-LCMS

7. Pre-formulation:

Investigation of physical and chemical properties of powdered form plants material, kinetic study, & compatibility with common excipients.

8. Formulation & Development of suitable dosage form.

9. Evaluation of formulated product by pre-clinical & clinical study.

5. IMPORTANCE OF THE STUDY:

Today the exploration and exploitation of the disease fighting properties of a multitude of photochemical found in both food and non-food plants have created a renaissance in human health and nutrition research.

I. INTERNATIONAL STATUS:

The WHO estimates that 347 million people worldwide have diabetes. The increasing incidence of CVD, the early age at which it manifests in these populations is also contributing to the high CVD burden. Thus in 1990, 46.7% of CVD-related deaths in developing countries occurred below the age of 70 years, in contrast to only 22.8% in the high-income industrial countries4. The Global Burden of Disease Study projected that 6.4 million deaths would occur due to CVD in the developing countries in 2020, in the age group of 30–69 years. MetS and its associated chronic diseases are public health concerns in the USA and worldwide. About 34% of US adults have MetS, and 9.3% of the US population (29.1 million) are diabetic.

II. NATIONAL STATUS:

According to recent estimates, cases of CVD may increase from about 2.9 crore in 2000 to as many as 6.4 crore in 2015, and the number of death from CVD will also more than double. Diabetes is also associated with an increased risk for CVD, and is emerging as a serious health challenge in India. Even though it accounted for only about 0.7% of India's disease burden in 1998, data suggest a significant load of diabetes cases in India—rising from 2.6 crore in 2000 to approximately 4.6 crore by 2015, and particularly concentrated in the urban population.(NCMH, Burden of Disease in India)

Distribution of diabetes in India, the National Urban Survey conducted across the metropolitan cities of India reported similar trend: 11.7 per cent in Kolkata (Eastern India), 6.1 per cent in Kashmir Valley (Northern India), 11.6 per cent in New Delhi (Northern India), and 9.3 per cent in West India (Mumbai) compared with (13.5 per cent in Chennai (South India), 16.6 per cent in Hyderabad (south India), and 12.4 per cent Bangalore (South India)

III. SIGNIFICANCE OF THE STUDY:

Research is needed to determine the role that nutrition & fitness, both singularly & together, play in maintaining body function including blood pressure, immune, skeletal muscular & other functions. Evolving research areas include prevention of disease related process, such as inflammation etc. Although medicinal therapy is effective in treatment of metabolic disorders at a very early stage, the side effects and resistance towards drug are a major problem. Plant has been used as medicine in treatment of metabolic disorders for thousands of years. However, the potential use of many plants as a source of new nutritional formulation for metabolic disorders is still poorly explored; only a small percentage has been investigated phytochemically. The extensive and systematic efforts are needed to put into the development of selective, potent, stable and safer novel nutritional formulation for metabolic disorders from the natural products.

6. PROPOSED WORK PLAN:

Sr. No.	WORK	PERIOD
1	Literature survey	6 months
2	Collection of plant materials	2 months
3	Extraction of plant materials	4 months
4	Phytochemical study	3 months
5	Pre-formulation study	1 months
6	Formulation & Development	6 months

7	Evaluation of pharmacological activity; pre-clinical study & clinical study	11 months
8	Other suggested work and compilation of data	3 months
	Total duration of work	36 month

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